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The Role of FSH in Prostate Cancer: A Case Report

Salvatore Catarinicchia*, E. David Crawford

University of Colorado, Division of Urology, 12631 E. 17th Avenue, C-305, Aurora, CO 80045, USA

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ABSTRACT

Castrate Resistant Prostate Cancer (CRPC) is a difficult entity to treat in the spectrum of prostate cancer disease. Recently, Follicle Stimulating Hormone (FSH) has been shown to play an important part in the natural history of prostate cancer disease progression (Crawford et al., 2014). Here, we discuss a now deceased 94 year-old patient who illustrates the importance of this.

Introduction

Castrate Resistant Prostate Cancer (CRPC) is a difficult entity to treat in the spectrum of prostate cancer disease. Recently, Follicle Stimulating Hormone (FSH) has been shown to play an important part in the natural history of prostate cancer disease progression.[1] Here, we discuss a now deceased 94 year-old patient who illustrates the importance of this.

Case report

History

EM is a 94 year-old male who initially presented to our clinic in 2009. He has a history of macular degeneration, osteoarthritis, abdominal aortic aneurysm and a radical retropubic prostatectomy in 1996 after workup showed elevated prostate specific antigen (PSA) and a positive biopsy showing Gleason 7 prostate cancer. Pathology following surgery revealed Gleason 4 + 5 = 9. He developed a rising PSA and had a biopsy proven Gleason 4 + 4 = 8 recurrence in his prostate bed in 1998. This leads to radiation and 6 cycles platinum based chemotherapy. He also had a bilateral orchiectomy in 1999 given his recurrence in an effort to suppress his testosterone levels. His PSA remained undetectable up until 2007, when it was found to be elevated to 10.0 ng/mL.

He was then seen in our multidisciplinary Urologic Oncology clinic given his biochemical failure and castrate resistant prostate cancer in 2009. He was initially placed on dutasteride and bicalutamide, however, his PSA continued to rise from 10 to 32.8 within the first 6 months of follow up. Given this, he was started on the LHRH antagonist degarelix in 9/2009. Throughout his course, bone scans remained negative for metastasis. Despite initiation of degarelix, his PSA slowly continued to rise, and in 2012, he was considered for additional, alternative therapies. When he developed a positive bone scan, provenge therapy was added in 1/2012 of which he received three infusions. He was then continued on androgen deprivation therapy with degarelix until 1/2014, at which time it was discontinued. Abiraterone was then started on 1/2015. Notably, his FSH started to rise again in this time, and degarelix was again restarted in 4/2015, which resulted in an FSH level that was <1 (see Table 1 as well as Fig. 1). Overall, the patient's PSA levels have come down with *combination* of abiraterone and degarelix, suggesting the influence of both testosterone and FSH on PSA levels (Fig. 2). He recently passed away secondary to complications of pneumonia, and autopsy was performed. His autopsy showed a focus of residual prostate adenocarcinoma, G 5 + 5 in a focus on lymph nodes subadjacent to the bladder on the right. There was also *no* evidence of bony metastasis, despite positive bone scan. The disease remained localized to the pelvis, suggesting direct extension or local metastasis of primary tumor. There were also small cell features upon further analysis and immunostaining of the tissue. Interestingly, his adrenals also showed cortical hyperplasia, possibly due to his hormonal therapies.

* Corresponding author.
E-mail address: salvatore.catarinicchia@ucdenver.edu (S. Catarinicchia).

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Investigations

Table 1
Various laboratory investigations launched during treatment course

	LH (mIU/mL)	FSH (mIU/mL)	PSA (ng/mL)	Testosterone (ng/dL)
2010	<1.0	2	36 → 29 → 62	38 → 45 → 27
2011	NR	NR	60 → 126	<20
2012	NR	NR	161 → 270	<20
2013	<0.2	2	373 → 481	<20
2014	8 → 11	22 → 25	610 → 697	<20
2015	10 → <0.2	27 → 30 → <1	293 → 178	<20

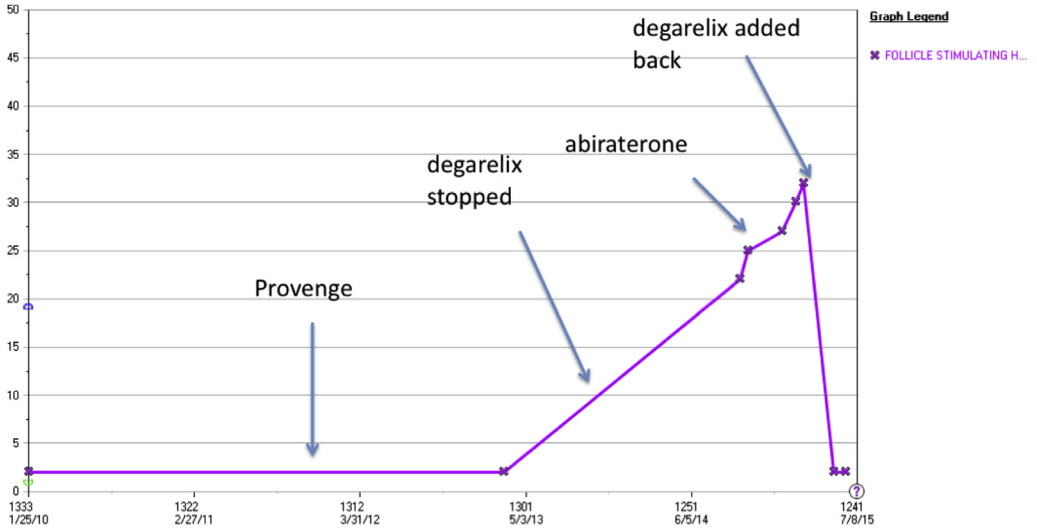

Figure 1. The effect of various therapies on FSH in our patient.

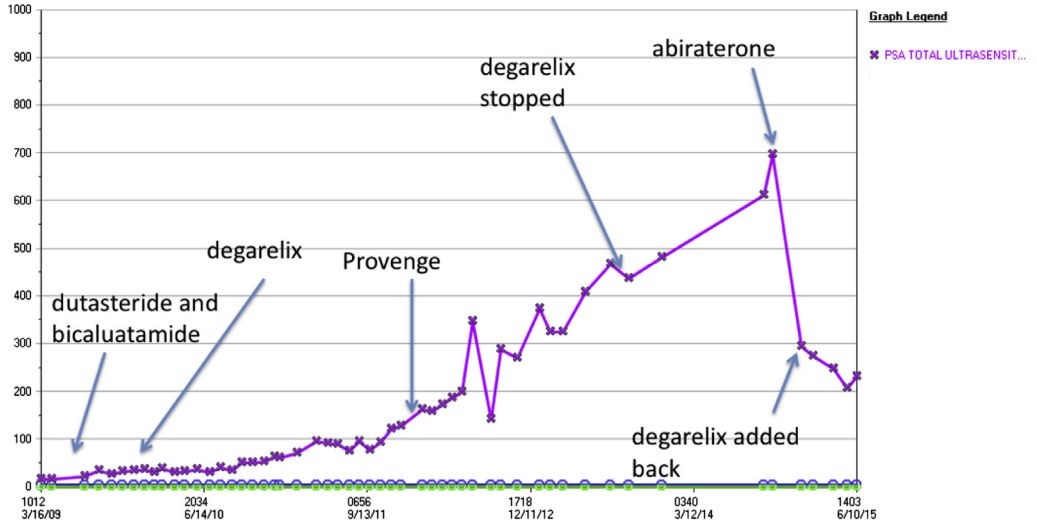

Figure 2. The effect of various therapies on our patient's PSA levels.

Discussion

The approach to evaluating and caring for the prostate cancer patient has become multi-modal, with new data and strategies entering the literature daily. One area of recent interest has been the involvement of the GnRH, FSH, and LH pathway and its role in prostate cancer. Multiple studies have shown that both benign and malignant human prostate cells produce both FSH and its receptor,[2–6] with a propensity for increased FSH receptor gene expression in malignant prostate cells.[4] Specifically, FSH may be important in tumor invasion, as evidenced by FSH receptor expression on the luminal endothelial surface found during intravasation.[6] Both the testes and prostate produce an important modulator of the FSH pathway, Prostatic Inhibin Peptide (PIP). PIP decreases FSH production and secretion from both the anterior pituitary and the prostate. Its role has been demonstrated in mouse models injected with castration-resistant CaP cells. Daily PIP treatment over 2 weeks significantly decreased tumor growth and FSH levels (38% and 60%, respectively), again demonstrating the importance of FSH and its physiologic effect on prostate cancer tumor growth.[7] This is important when considering bilateral orchiectomy, such as our patient had, as elimination of PIP from the hormonal pathway would then lead to largely unregulated FSH levels and the subsequent physiologic effects of FSH on prostate cancer cells.

Notably, our patient had an increased testosterone level despite bilateral orchiectomy when he established care with our clinic. This may be explained by both adrenal sources of testosterone, as well as production by castrate resistant prostate cancer cells themselves. Several recent studies have shown that intratumoral production of testosterone can occur, and is the therapeutic rationale behind medications such as abiraterone and enzalutamide in advanced castration resistant prostate cancer.[8–10]

The effects of a GnRH antagonist were clearly demonstrable in our patient. His FSH level was largely undetectable, until ADT was held for 1 year, at which time his FSH and LH rose, with a dramatic increase in PSA during that time as well. Notably, his testosterone levels remained less than 20 during that time, suggesting the mitogenic effects of FSH on prostate cancer cells in the setting of little to no testosterone detected in serum. Additionally, his FSH levels came down to less than 1 when restarted on his GnRH antagonist, along with his PSA.

The presence if Gleason $5 + 5 = 10$ prostate cancer on autopsy illustrates the importance of obtaining negative margins during surgical resection, as well as a thorough lymph node dissection in aggressive disease. The presence of Gleason 10 suggests the long term effect of untreated castrate resistant cancer, as the histology was more advanced than his initially pathology from his first surgery. This focus may also be responsible for increased testosterone levels despite bilateral orchiectomoy. Overall, the autopsy in this patient was an important addition in understanding his specific disease, and particular response to various treatments. This could be employed more frequently as we aim to understand disease response to novel therapeutics.

In short, a patient centered, disease specific approach can be useful when treating prostate cancer. Future research tailored to understanding disease response to manipulation of the hormonal milieu will be helpful in providing tailored care based on an individual's disease and its specific response to hormones. Additionally, post mortem analysis can be useful in understanding response to novel therapeutics. Despite increasing the complexity of treatment paradigms, novel therapies such as LHRH antagonists are welcome additions to the urologic oncologist's armamentarium.

Conflict of interest

The authors express no conflict of interests.

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